

Claims

1. 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt and crystalline forms thereof.
2. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A, characterized by a triclinic unit cell with parameters:
 $a = 8.6 \text{ \AA}$, $b = 18.7 \text{ \AA}$, $c = 15.8 \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 113^\circ$, $\gamma = 90^\circ$.
3. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:
- | Form A | | |
|-----------------------------|-----------------------------|-----------------------------|
| d-value
(\AA) | d-value
(\AA) | d-value
(\AA) |
| 11.4 | 5.7 | 3.92 |
| 9.3 | 4.72 | 3.18 |
| 7.8 | 4.35 | |
4. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A, characterized in providing a Raman Spectrum exhibiting substantially the following relative intensities above 18.6:

Raman shift (cm ⁻¹)	Relative intensity	Raman shift (cm ⁻¹)	Relative intensity
2935.9	56.2	1042.3	41.6
1671.2	31.8	877.6	33.6
1617.7	56.6	781.7	28.1
1597.2	35.8	708.6	18.6
1590.4	39.4	554.9	23.7
1533.9	26.3	542.8	22.3
1484.4	22.6	535.7	25.9
1427.1	100.0	501.2	29.9
1415.8	85.8	379.6	25.2
1392.9	46.7	352.9	22.6
1383.1	55.8	338.1	28.8
1296.2	20.1	268.3	22.3
1271.1	25.5	239.7	39.8
1258.2	42.0	228.2	33.2
1095.5	21.5	196.8	26.6
1059.7	20.4		

5. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form B, characterized by a triclinic unit cell with parameters:

$$a = 8.4 \text{ \AA}, b = 14.2 \text{ \AA}, c = 19.9 \text{ \AA}, \alpha = 93^\circ, \beta = 100^\circ, \gamma = 97^\circ.$$

6. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form B, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form B		
d-value (Å)	d-value (Å)	d-value (Å)
11.8	8.3	4.72
11.1	5.9	4.52
9.8	5.5	

7. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form B, characterized in providing a Raman Spectrum exhibiting substantially the following relative intensities above 18.6:

Raman shift (cm ⁻¹)	Relative intensity	Raman shift (cm ⁻¹)	Relative intensity
2937.4	53.5	1100.1	21.9
2928.8	41.9	1040.8	50.7
1671.4	33.5	964.9	18.6
1617.0	47.9	888.2	34.4
1590.3	39.1	871.9	28.4
1533.8	20.9	777.4	31.6
1480.7	20.9	751.4	19.1
1461.0	21.4	710.3	18.6
1426.4	81.9	553.1	26.0
1417.3	100.0	536.1	26.5
1394.4	50.2	501.3	31.2
1383.1	59.1	382.3	22.3
1357.5	20.9	353.1	25.6
1305.8	24.7	335.5	32.1
1280.3	19.1	285.4	22.8
1254.9	55.8	241.1	41.4
1163.5	22.8	198.9	22.3

8. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form C, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form C		
d-value (Å)	d-value (Å)	d-value (Å)
13.1	5.7	3.57
10.7	4.88	3.51
6.8	4.39	

9. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form D, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form D		
d-value (Å)	d-value (Å)	d-value (Å)
13.8	6.4	3.55
9.1	5.1	2.38
6.9	4.62	

10. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form D, characterized by a triclinic unit cell with parameters:
 $a = 8.6 \text{ Å}$, $b = 15.9 \text{ Å}$, $c = 19.4 \text{ Å}$, $\alpha = 70^\circ$, $\beta = 89^\circ$, $\gamma = 75^\circ$.

11. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form E, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form E		
d-value (Å)	d-value (Å)	d-value (Å)
12.5	6.1	3.88
10.1	5.1	3.71
9.5	4.61	

12. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form F, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form F		
d-value (Å)	d-value (Å)	d-value (Å)
13.5	5.8	3.70
7.9	5.0	3.63
6.9	3.96	

13. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form G, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form G		
d-value (Å)	d-value (Å)	d-value (Å)
13.6	6.4	3.82
10.1	5.7	3.61
9.2	5.1	

14. A compound according to claim 1 wherein the crystalline form is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form H, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form H		
d-value (Å)	d-value (Å)	d-value (Å)
11.1	6.3	3.84
8.0	5.4	3.59
7.1	4.01	

15. 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt, characterized in being a mixture of two or more of the crystalline forms of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt defined in claims 2 to 14.
16. 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt, characterized in being a mixture of form A and form B.
17. 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt, characterized in being a mixture of two or more of form A, form B and form H.

18. A process for the preparation of form A as defined in any of claims 2 to 4 comprising the steps of:
- a) dissolving or suspending 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide in a suitable solvent;
 - b) adding methanesulfonic acid at a higher temperature;
 - c) allowing the solution or suspension to crystallize; and
 - d) isolating the form A thus obtained.
19. A process for the preparation of form B as defined in any of claims 5 to 7 comprising the steps of:
- a) dissolving or suspending 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide in a suitable solvent;
 - b) adding methanesulfonic acid at a lower temperature;
 - c) allowing the solution or suspension to crystallize; and
 - d) isolating the form B thus obtained.
20. A process for the preparation of form A as defined in any of claims 2 to 4 comprising the steps of:
- a) dissolving or suspending any form of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt in a suitable solvent;
 - b) allowing the solution or suspension to crystallize at higher temperature, optionally using form A to induce crystallization; and
 - c) isolating the form A thus obtained.
21. A process for the preparation of form B as defined in any of claims 5 to 7 comprising the steps of:
- a) dissolving or suspending any form of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt in a suitable solvent;

- b) allowing the solution or suspension to crystallize at a lower temperature, optionally using form B to induce crystallization; and
- c) isolating the form B thus obtained

- 5 22. A process for the preparation of form A according to claim 20 wherein the form of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt is form B.
- 10 23. A process for the preparation of form B according to claim 21 wherein the form of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt is 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A.
- 15 24. A process according to any of claims 18 or 19, characterized in that seeds are added to the solution or suspension to induce crystallization.
25. A process according to any one of claims 18, 20, 22 and 24 wherein the higher temperature is a temperature of 40 °C or above.
- 20 26. A process according to any one of claims 19, 21, 23 and 24 wherein the lower temperature is a temperature lower than 40 °C.
- 25 27. 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A or form B prepared according to any of claims 18 to 26.
- 30 28. A pharmaceutical formulation comprising at least one of the crystalline forms of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt as defined in any one of claims 1 to 14 in admixture with at least one pharmaceutically acceptable excipient.

29. Use of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt as defined in any one of claims 1 to 14 in therapy.
- 5 30. The use of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt as defined in any one of claims 1 to 14 as active ingredient in the manufacture of a medicament for use in treatment or prevention of gastrointestinal disorders.
- 10 31. The use in accordance with claim 30 wherein the gastrointestinal disorders are gastrointestinal inflammatory diseases or gastric acid-related diseases
32. The use in accordance with claim 30 wherein the gastrointestinal inflammatory diseases or gastric acid-related diseases are gastritis, gastric ulcer, duodenal ulcer,
15 peptic ulcer diseases, reflux esophagitis, Zollinger-Ellison syndrome, gastrinomas, acute upper gastrointestinal bleeding.
33. The use in accordance with claim 30 is in treatment or prevention of Gastroesophageal Reflux Disease (GERD) symptoms, heartburn, regurgitation, acid
20 reflux disease requiring short and long-term management, sleep disturbance due to silent gastro-esophageal reflux, *Helicobacter pylori* eradication, nausea, vomiting due to chemotherapy or post-operative conditions, and stress ulceration.
34. The use in accordance with claim 30 is in treatment or prevention of Gastroesophageal
25 Reflux Disease (GERD) symptoms includes healing of erosive esophagitis, symptomatic GERD, maintenance of healed erosive esophagitis, and long term management of symptomatic GERD.
35. The use in accordance with claim 30 is in treatment or prevention of airway disorders.
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36. The use in accordance with claim 35 wherein the airway disorder is bronchitis, COPD, asthma, pneumonitis, pulmonary fibrosis, acid aspiration and acid asthma.

37. A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt as defined in any of
5 claims 1 to 14, to a patient suffering therefrom.